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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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KLAUS J. BACH & ASSOCIATES
4407 TWIN OAKS DRIVE
MURRYSVILLE, PA 15668

| EXAMINER |
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SULLIVAN, DANIEL M

| ART UNIT | PAPER NUMBER |
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1636

DATE MAILED: 04/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/051,804

Applicant(s)

ANGEL ET AL.

Examiner

Daniel M Sullivan

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 is/are pending in the application.
- 4a) Of the above claim(s) 1-5 (in part) is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. 09/679,695.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 11 January 2002 as a continuation-in-part of U.S. Patent Application 09/679,695 filed 5 October 2000, which is a continuation-in-part of international patent application PCT/EP99/01805 filed 03/18/99 and claims the priority of German application 198 15 331.7 filed April 06, 1998. The preliminary amendment filed 9 December 2002 has been entered. Claims 1-5 are pending, claim 1 was amended in the 9 December Paper.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-5 as they read on a transcription factor comprising SEQ ID NO: 21) in the Paper filed 9 April 2004 is acknowledged. The traversal is on the ground(s) that, as a member of the Patent Cooperation Treaty, the US is held essentially to adhere to the PCT requirements of Article 27. This is not found persuasive because the instant application is filled under 35 USC 111 and therefore subject to restriction according to 35 USC 121, 37 CFR 1.141 and 37 CFR 1.142 (see MPEP chapter 800).

Claims 1-5 as they read on a transcription factor comprising SEQ ID NO: 22-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In the instant case, the specification and claims of the 09/679,695 application provide no support for the limitation “valine being replaceable by alanine, leucine, methionine, isoleucine, glutamine” recited in claim 1. Although claim 1 of the 09/679,695 application recites the limitation “valin [sic] being replaceable by another neutral amino acid”, the specific subgenus of neutral amino acids recited in the instant claims (*i.e.*, alanine, leucine, methionine and glutamine) is not explicitly or implicitly contemplated in the parent application. Therefore, the claims are afforded an effective filing date of 11 January 2002.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-5, as written, do not sufficiently distinguish over transcription factors as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. Although the

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transcription factor of the claims is limited to comprising variation of a known naturally occurring amino acid sequence, it is reasonable to expect that the claimed transcription factor occurs naturally by spontaneous mutation. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, *e.g.*, by insertion of “Isolated” or “Purified”. See MPEP 2105.

Claims 3-5 are rejected under 35 U.S.C. 101 because the claimed recitation of a use (*e.g.*, the manufacture of a therapeuticum), without setting forth any steps involved in the process, results in an improper definition of a process, *i.e.*, results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The elected invention is directed to a transcription factor comprising a basic domain and an adjacent Leucine zipper domain comprising the sequence: LKXKXXXLKXLXXX'XLAXTXXXLRXQXXXLK. Thus, the claim is directed to a transcription factor comprising a leucine zipper domain described by the general formula $L-(X)_6-L-(X)_7-L-(X)_6-L-X$.

State of the prior art and level of predictability in the art: The art teaches the canonical leucine zipper domain sequence $L-(X)_6-L-(X)_6-L-(X)_6-L$. For example, Hirst *et al.* (1996) *Protein Eng.* 9:657-62 teaches, "[t]he leucine repeat, Leu- X_6 -Leu- X_6 -Leu- X_6 -Leu (where X may be any residue), occurs in all leucine zippers in the SWISS-PROT database" (sentence bridging pages 657-658). Thus, the instant claims are directed to a transcription factor comprising a single amino acid insertion in the middle of a leucine zipper domain.

The art generally acknowledges that the effect of modifying amino acid sequence on the function of a polypeptide is highly unpredictable. For example, Richards (1997) *Cell Mol. Life Sci.* 53:790-802 teaches, "[i]n terms of structural alterations and thermostability, responses to

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genetic mutations are context dependent and remain difficult to predict with any confidence” (abstract, column 1). Thus, Richards teaches that the effect of mutation on protein stability, a prerequisite for biological function, is unpredictable. Richards also teaches that even limited amino acid modifications can have dramatic effects on protein structure and function. In the second column on page 791, Richards cites the example of influenza virus hemagglutinin protein, wherein alterations in the ionization state of just a few ionizable groups dramatically alters the biological behavior of the molecule. Citing a published study of done on the gene V protein, Richards teaches that, in spite of only limited modification at two amino acid positions, “[t]he effects on the overall stability of the protein were remarkably variable” (page 794, column 1). In the paragraph bridging pages 796 and 797, Richards teaches, “[i]n single site mutants, the structural changes are generally greatest near the site of mutation, and moving away, decrease radially in all directions. *Even the small changes are so complex that the linkage relations do not allow assignments of the energetic changes to unique parts of the altered residue and its immediate contacts*” (emphasis added) and “[t]here is no convincing explanation yet of how the changes in binding can produce a major movement over such a distance.” Finally, in the first full paragraph in the second column on page 793, Richards teaches, “[a]lmost all mutations are accompanied by some conformational change, making prediction of the effects on stability difficult. *In most cases mutations lead to lowering of the stability.*” (emphasis added). Thus, Richards teaches that small changes in the primary structure of a protein frequently have dramatic effects on the higher order structure and function of the protein, and that these effects are highly unpredictable.

Given the general unpredictability of the effect of amino acid modification on protein function and the highly conserved nature of the relative position of leucines within a leucine zipper domain, the skilled artisan could not readily predict what the functional characteristics of the claimed transcription factor.

Amount of direction provided by the inventor and existence of working examples: The instant disclosure provides several working examples of modified c-Jun and ATF2 transcription factors comprising amino acid substitutions at several positions within the leucine zipper domain. However, all of the examples comprise the canonical L-(X)₆-L-(X)₆-L-(X)₆-L-X structure and there are no examples of a transcription factor comprising the sequence L-(X)₆-L-(X)₇-L-(X)₆-L-X. Thus, the disclosure provides no guidance as to the functional characteristics of the claimed transcription factor.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to use the claimed invention without first engaging in undue empirical experimentation to determine the functional characteristics of the claimed transcription factor. The specification contemplates a variety of general uses for the claimed invention; however, applying the claimed transcription factor to any of these uses requires that the skilled artisan know the functional characteristics of the transcription factor. Given the unusual modification of the leucine zipper domain, the art recognized unpredictability of such a modification on protein function and the absence of working examples, the skilled artisan would have to engage in undue experimentation to uncover the useful properties of the claimed invention. Therefore, the disclosure fails to provide adequate enablement for the claimed subject matter.

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite in the recitation of “the transactivation domain”. There is no antecedent basis for the limitation in the claims.

Claims 3-5 provides for the use of the transcription factor of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Alternatively, it is possible that Applicant is attempting to indicate some structural limitation of the transcription factor by reciting an intended use. However, it is unclear from the disclosure how a transcription factor for the manufacture of a therapeuticum would differ from a transcription factor for the testing of indications.

Claim 3 is further indefinite in the recitation of “therapeuticum”. The term is not conventional in the English language and is not explicitly defined in the specification. Therefore, the metes and bounds of the term are unclear.


Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DMS


DAVID GUZMAN
PRIMARY EXAMINER